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Review

Loss of appetite, weakness and chronic fatigue: current approach

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ABSTRACT

Fatigue and chronic fatigue are frequently encountered complaints in clinical practice, and their etiology is difficult to determine. In addition to increasing patient dissatisfaction due to the lack of clarification of the etiology, it brings about a significant increase in cost due to the fact that patients consult multiple physicians. In this review, current clinical practices, including especially overlooked points in the etiology of weakness and fatigue, investigations that should be planned, diagnosis, treatment, and lifestyle recommendations, are reviewed.

Keywords: Loss of appetite, weakness, fatigue, chronic fatigue syndrome

LOSS OF APPETITE

Appetite is generally defined as the desire for food and is known as a common symptom encountered by physicians. It can manifest itself as a consequence of many clinical conditions and can lead to patient dissatisfaction and inadequate treatment compliance.

Appetite is regulated by hormonal effects. Ghrelin, known as the appetite hormone, is generally responsible for appetite regulation. Ghrelin is a peptide hormone that is mainly produced in the gastric fundus.[1] In addition to appetite regulation, ghrelin is also effective for energy homeostasis and carbohydrate metabolism.[2]

Many organic causes of anorexia have been described. However, it is not possible for clinicians to rule out all these causes. Therefore, a detailed anamnesis and physical examination should be performed, and the underlying etiology should be determined according to the accompanying symptoms and findings. The most common causes of anorexia are summarized in Table 1.[3]

Table 1. Common causes of loss of appetite

• Acute or chronic infections
• Gastroesophageal reflux, *H. pylori* infection
• Dyspepsia
• Nausea, vomiting
• Diarrhea, constipation
• Gastroenteritis
• Intestinal parasitoses
• Dysphagia
• Anemia (especially iron deficiency anemia)
• Zinc deficiency
• Acute renal failure
• Psychological reasons

WEAKNESS AND FATIGUE

Chronic fatigue and weakness are common complaints frequently encountered by all clinicians and often difficult to treat. The main reason for the difficulty in its treatment is the difficulty in making the diagnosis that leads to the clinical presentation. The reason for this situation is that it can occur as a result of many organic and psychiatric disorders. On the other hand, weakness and chronic fatigue can be observed without any underlying disease.

Weakness and chronic fatigue are complaints frequently encountered in all health institutions, especially among primary care physicians. Even a large proportion of patients presenting with other complaints complain of weakness and fatigue. In studies, it was found that these complaints were present in patients presenting to outpatient clinics at rates ranging between 10% and 40%.[4]

Basic evaluation and routine investigations are performed on patients with complaints of weakness and chronic fatigue. As a result of the examinations, no pathology is usually detected, psychological causes are considered, and patients are referred to psychiatry physicians. This significantly increases the workload of psychiatric physicians. Moreover, the examinations performed on these patients do not detect any psychiatric problems in a large proportion of them. In addition to the workload for the physicians, this situation is also annoying for the patients.[4,5]

The increase in workload does not only affect psychiatric physicians. These patients, for whom no clear diagnosis can be made, are referred to a wide variety of specialty physicians and cause an increase in the workload of all clinicians. Studies have shown that nearly 50% of patients with complaints of weakness and chronic fatigue are seen by five specialty physicians. However, many of them still remain inconclusive.

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Patients' daily lives and work performances are also negatively affected because their complaints do not go away.[5]

At this point, patients' expectations from physicians are that a clear diagnosis should be made, preferably a pharmacologic treatment should be initiated, and all complaints should disappear in a short time. However, as mentioned, in the majority of these patients, even a treatable organic cause cannot be detected.[5,6]

As the duration of fatigue and weakness increases, the frequency of patients being psychologically affected by this condition increases, and some long-term side effects are observed in patients. Long-term side effects that occur in these patients over time are summarized in Table 2.[6]

Table 2. Long-term side effects in people with weakness and chronic fatigue

Common muscle and joint pains	Depression and anxiety
Exhaustion after physical activities	Sexual dysfunction
Headaches with a new onset	Decreased sleep quality
Impaired memory and concentration	≥30.00

Another important problem for patients with complaints of weakness and chronic fatigue is deciding which specialty physician to consult. These complaints may be the initial symptoms of diseases, followed by many branches, thus requiring a holistic perspective. The branch with this holistic perspective is primarily family physicians, while internal medicine specialists are preferred as another option for adults.[5-7]

DIAGNOSTIC EVALUATION

As in almost all branches of medical practice, the first approach for patients with complaints of weakness and chronic fatigue should be anamnesis and physical examination. With a detailed and careful physical examination, many diagnostic clues can be found. It should be kept in mind that conditions such as musculoskeletal problems, lumbar and cervical disc herniation, osteoarthrosis, and fibromyalgia, which can be detected by physical examination, may cause intensity and severe fatigue.[7]

After a detailed anamnesis and physical examination, initial investigations must be ordered. In patients presenting with weakness and chronic fatigue, initial investigations should include a complete blood count, blood biochemistry, CRP, sedimentation level, thyroid hormone level, vitamin D, vitamin B12, urinalysis, PA chest radiography, and ECG if necessary. If significant pathologies are detected in these tests, further investigations should be planned. Initial evaluation tests and conditions that may be relevant are summarized in Table 3.[8]

ETIOLOGY

Many diseases and factors have been identified as the etiologies of chronic fatigue and weakness. The general diagnostic approach is based on the exclusion of many of these causes. It has been shown that less than 20% of the etiologic causes identified are due to organic pathologies. Approximately 80% are psychological and lifestyle-related conditions. Psychological and lifestyle-related conditions are summarized in Table 4.[9]

Table 3. Initial evaluation tests for weakness and fatigue and related conditions

Complete blood count	In particular, about 1/3 of women of reproductive age are anemic. Anemia is one of the leading causes of fatigue and weakness.
Blood biochemistry test	Abnormalities in liver function tests and enzyme elevations may present with weakness and fatigue depending on the cause. Gilbert's syndrome with elevated indirect bilirubin is also a common cause. Renal function tests and electrolyte disorders, especially hyperpotassemia, may also cause these complaints.
Hormone tests	Especially thyroid hormone disorders, Addison's disease with cortisol deficiency, and pituitary insufficiency should be investigated. First of all, TSH should be requested, and morning fasting plasma cortisol levels should be checked in suspicious cases. Vitamin B12, folic acid, and vitamin D levels should also be checked. Deficiencies of these are common causes of weakness and fatigue. These symptoms may be observed in patients with a history of diabetes and prediabetes due to insulin resistance and high blood sugar. HBA1c, insulin level, and OGTT should be requested if necessary.
Other	P-A chest radiography, ECG, complete urinalysis, CRP, and erythrocyte sedimentation rate should be ordered if not taken recently. In patients with symptoms and signs, USG of the whole abdomen should be ordered if necessary.

Table 4. Psychological and lifestyle-related conditions that may cause fatigue and weakness

Psychological disorders and mood disorders	It is caused by all psychological disorders, especially depression.
Eating disorders	It is observed in all disorders, primarily due to anorexia and bulimia.
Sleep disorders	Insomnia and obstructive sleep apnea syndrome
Unhealthy lifestyle	Work problems, economic problems, sedentary life, lack of regular exercise, inadequate and unhealthy diet, smoking, alcohol use, insufficient rest
Drug and substance use	Alcohol, caffeine, psychotropic drugs, antihistamines, cardiovascular drugs, reserpine, methyldopa

Obstructive sleep apnea syndrome is a syndrome that develops due to upper airway obstruction during sleep. It is characterized by intermittent awakenings, decreased oxygen saturation, decreased sleep quality, fatigue, and daytime sleepiness. The most prominent risk factors include male gender, obesity, alcohol and smoking, endocrine disorders, and family history.[10,11] The organic causes of chronic fatigue and weakness are compiled in Table 5, and they account for less than 20% of the identified causes.

Table 5. Organic causes of fatigue and weakness

Infections	Viral, bacterial, etc.
Metabolic disorders	Diabetes, thyroid dysfunction, pituitary insufficiency, Addison's disease, etc.
Hematologic diseases	Anemia, leukemia, metal intoxications
Renal diseases	Acute and chronic renal failure
Liver diseases	
Rheumatologic diseases	Fibromyalgia, Sjögren's syndrome, polymyalgia rheumatica, giant cell arteritis, polymyositis and dermatomyositis, inflammatory bowel disease, sarcoidosis, chronic fatigue syndrome, etc.
Neurological diseases	Parkinson's disease, multiple sclerosis, etc.
Cardiac problems	Coronary artery disease, congestive heart failure
Respiratory system diseases	Chronic obstructive pulmonary disease, asthma, etc.

CHRONIC FATIGUE SYNDROME

Chronic fatigue syndrome (CFS) is a disease that is often overlooked in etiology and requires detailed questioning. Chronic fatigue syndrome can be defined as a disease that lasts longer than 6 months, increases with exertion, has an unexplained cause, and may progress with impairment in daily activities and cognitive functions. It has been found that up to 2 million people in the USA are affected by this condition; it is more common in women than in men, and it is usually found in other family members.[12,13]

Although the etiology and pathophysiologic mechanisms of the disease have not been clearly demonstrated, there are conditions thought to be effective. These can be listed as infectious causes, immune system disorders, and hormonal disorders.[14-17]

Although the diagnosis is basically based on the exclusion of all other causes, diagnostic criteria have been determined by guidelines. The diagnostic criteria for CFS are compiled in **Table 6**.[18]

Table 6. Diagnostic criteria for chronic fatigue syndrome

At least three of these symptoms are required for a diagnosis:
• Fatigue lasting more than 6 months, of recent onset, not restricted by exertion, and not demonstrated by exercise tests
• Restriction in professional, educational, social, and personal activities compared to the period before the disease
• Fatigue after exertion
• Inability to rest with sleep
At least one of the following symptoms is also required for diagnosis:
• Cognitive impairment
• Orthostatic intolerance

Laboratory tests are usually normal in CFS. The aim is to rule out all other pathologic conditions. Although there is no specific treatment for CFS, symptomatic and non-treatment therapies may be recommended.

Early diagnosis of organic causes of chronic fatigue can significantly improve the patient's quality of life by enabling diagnosis and treatment of the underlying medical condition. Some tips to help early diagnosis: Fatigue lasting longer than six months, accompanied by other symptoms (fever, weight loss, muscle aches, joint pains, sleep problems, difficulty concentrating), presence of risk factors (family history of chronic disease, weak immune system).[19,20]

RECOMMENDATIONS FOR WEAKNESS AND CHRONIC FATIGUE

In these patients, treatment of the underlying conditions should be planned first. However, since a significant etiology cannot be detected in most of them, symptomatic treatments, lifestyle changes, and exercise are recommended. Nonsteroidal anti-inflammatory drugs are especially recommended as symptomatic treatments. Possible recommendations for these patients are summarized in **Table 7**.[21-23]

Table 7. Recommendations for patients with weakness and chronic fatigue

• Eating patterns, sleep patterns, and regular exercise
• Avoiding inadequate and unhealthy nutrition, reaching and maintaining the ideal weight
• Recommendations for adequate rest and quality sleep
• Gradual transition away from sedentary life to regular active exercise
• Approaches to work problems that cause serious anxiety and psychiatric support, if necessary
• Suggestions for adjustments to household expenditures and the economic situation
• Suggestions for organizing social activities and friendships
• Recommendations for balancing mental health

CONCLUSION

Weakness, fatigue and loss of appetite are among the most common applications to outpatient clinics in clinical practice. We tried to summarize current clinical practices, including the points to be considered in the etiology of this condition, the examinations to be planned, diagnosis, treatment and lifestyle recommendations.

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